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(54) **Title:** 3-CYCLOPENTYLOXY-4-METHOXYPHENYL-ISOTHIAZOLINONE DERIVATIVES AND THE USE THEREOF

(57) **Abstract:** This invention relates to novel compounds of 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives having the activity to inhibit tumor necrosis factor-α (TNF-α) or cyclic AMP phosphodiesterase IV (PDE 4). In more detail, this invention is directed to the preparation processes of the novel compounds of formula [1], and a pharmaceutically acceptable salt thereof, and pharmaceutical compositions possessing important biological therapeutic effect on inflammatory and autoimmune diseases associated with a detrimental excess of TNF-α.

3-CYCLOPENTYLOXY-4-METHOXYPHENYL-ISOTHIAZOLINONE DERIVATIVES AND THE USE THEREOF

TECHNICAL FIELD

The present invention relates to novel compounds of formula [1] which inhibit Tumor necrosis factor-α (TNF-α) or the enzymatic activity of cyclic AMP phosphodiesterase IV (PDE 4). These compounds may be useful in prevention or treatment of arthritis, bronchial asthma, bronchitis, chronic atretic airway, psoriasis, allergic rhinitis, dermatitis, AIDS, Crohn's disease, septicemia, septic shock, other inflammatory diseases such as cachexia, graft versus host reaction, multiple sclerosis, systemic Lupus Erythematosus, etc. The invention is also directed to the preparation of these compounds, pharmaceutical compositions containing these compounds and methods for their pharmaceutical use.

BACKGROUND ART

TNF-α is a primary cytokine secreted by mononuclear phagocytes stimulated by several immune activators. These factors are known to induce acute infection, shock, inflammation, heat, hemolysis, coagulation and acute reaction in human or animal.

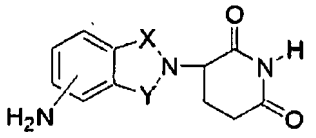
If TNF-α is excessed or not regulated well, many diseases like endotoxemia, toxic shock syndrome [Nature 330. 662-664(1987)] or cachexia [Lancet 335(1990), 662 (1990)] occur. Therefore, TNF-α inhibitor is now being studied extensively for therapeutics against the above diseases. Recently, a soluble receptor for TNF-α and an anti-TNF antibody were approved by FDA and demonstrated for the striking potency in human rheumatoid arthritis patients. Although rolipram has CNS side effects like nausea and vomiting [Drugs of the Future 28. 793-803(1995)], it provides an active pharmacophore currently being studied as novel derivatives for inhibition of TNF-α [WO9212961, WO9503794,

WO9402465, WO9505386, WO9509624, WO9620926].

PDE 4 is an enzyme that specifically hydrolyzes cAMP into inactive adenosine 3',5'-monophosphate. The cAMP has been shown to be a second messenger mediating the cellular responses to external stimuli and to act as relaxing or contradicting bronchial muscles.

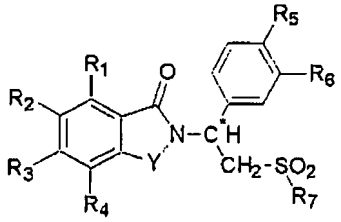
The inhibition of PDE 4 leads to the prevention of broncospasm by maintaining the concentration of cAMP and also induces an anti-inflammation. Therefore, compounds that inhibit PDE 4 should be effective in treating asthma and the like diseases.

United states patent application publication No. US 5,635,517 discloses that isoindolinone compounds of the formula



wherein one of X and Y is C=O and the other of X and Y is C=O or CH_2, exhibit TNF-α-reducing activity. US 5,635,517 does not disclose or suggest compounds wherein the isoindolinone moiety is bonded phenyl moiety.

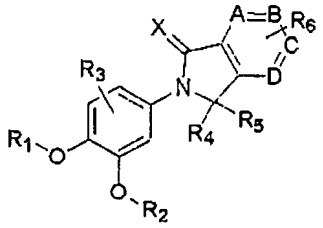
United states patent application publication No. US 6,020,358 discloses that isoindolinone compounds of the formula



wherein Y is C=O, CH_2, SO_2, or $CH_2C=O$ exhibit TNF-α-reducing activity. US 5,635,517 does not disclose or suggest compounds wherein the isoindolinone moiety is bonded directly 3,4-dialkoxyphenyl moiety.

WO Patent Application No. 98/42666 that is our previous patent discloses

that 3,4-dialkoxyphenyl derivatives are inhibitor of TNF-α release, but does not disclose or suggest that the compound inhibits PDE 4 and R_6 is a substituted isoindoilnone ring.



Therefore, it is expected that compounds with the inhibitory activity against PDE 4 or TNF-α will be pharmaceutically valuable and there is always a need to develop new compounds which inhibit PDE 4 and TNF-α

The object of the present invention is directed to a compound that inhibits PDE 4 and TNF-α.

DISCLOSURE OF INVENTION

The inventors have studied extensively to settle the problems that the previous PDE 4 or TNF-α inhibitors possess. As a result, the novel 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives depicted in formula [1] have shown selective and potent PDE 4 and TNF-α inhibitor. We elucidated that they had no side effect like nausea, or vomiting. And hence we have achieved this invention.

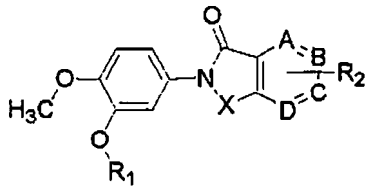
The first aim of this invention presents the novel compounds with potent PDE 4 and TNF-α inhibition activity represented in formula [1].

The second aim of this invention presents the methods of synthesis of the novel 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives and their salts in formula [1].

The third aim of this invention presents pharmaceutical compositions of PDE 4 and TNF-α inhibitor containing the novel 3-cyclopentyloxy-4-

methoxyphenyl-isothiazolinone derivatives and their salts in formula [1] as use of joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, allergic inflammation, and autoimmune diseases.

This invention provides the compound formula [1] of the novel 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives and a pharmaceutically acceptable salt thereof.



where in

R1 is lower alkyl, cycloalkyl, hydroxycycloalkyl, arylalkyl, cycloalkylalkyl, bicycloalkyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

Definition

"Halogen" means fluoro, chloro, or bromo. Preferred are fluoro and chloro.

"Lower alkyl" means aliphatic hydrocarbon group having 1 to 6 carbon atoms in the chain such as methyl, ethyl, propyl, butyl, pentyl and hexyl. Preferably, it means straight or branched hydrocarbon having 1 to 4 carbon atoms.

"Lower alkoxy" means alkyl oxy group that may be straight or branched having 1 to 4 carbon atoms in the chain such as methoxy, ethoxy, propoxy and butoxy.

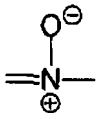
"Cycloalkyl" means non-aromatic mono- or multicyclic ring system having 3 to 8 carbon atoms in the chain such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl and adamantyl. Preferably, it means hydrocarbon having 3 to 6 carbon atoms.

"Arylalkyl" means phenyl alkyl group having 3 to 10 carbon atoms in the chain such as phenylethyl, phenylpropyl, phenylbutyl and phenylpentyl. Preferably, it means hydrocarbon having 3 to 8 carbon atoms.

"Cycloalkylalkyl" means cycloalkylalkyl group in which cycloalkyl is as previously defined, alkyl is methyl and ethyl. Preferably, cycloalkylalkyl is cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, and cyclopentylethyl.

"Bicycloalkyl" means indanyl group such as 1-indanyl and 2-indanyl.

"N-oxide" means a moiety of the following structure



According to a compound aspect of the invention, preferred compounds described formula [1] are following:

wherein

R1 is C_1-C_4 lower alkyl, C_3-C_6 cycloalkyl, hydroxy-C_3-C_6 cycloalkyl, aryl-C_3-C_8 alkyl, cycloalkyl-C_1-C_2 alkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, amino, C_1-C_4 lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, C_1-C_4 lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

According to a compound aspect of the invention, more preferred compounds described formula [1] are following:

wherein

R1 is C_1-C_2 lower alkyl, C_3-C_6 cycloalkyl, hydroxy C_3-C_6 cycloalkyl, aryl C_3-C_6 alkyl, C_3-C_5 cycloalkyl C_1-C_2 alkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, amino, C_1-C_4 lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, C_1-C_2 lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

Preferred compounds for use according to the invention are selected from the following:

2-(3-Cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-benzo[d]isothiazol-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

2-(3-sec-Butoxy-4-methoxyphenyl)-isothiazolo[5,4-c]pyridin-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-isothiazolo[4,5-c]pyridin-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-isothiazolo[5,4-b]pyridin-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-isothiazolo[4,5-b]pyridin-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-5-iminomethyl-1-oxo-1,2-dihydro-1λ^4-isothiazol-3-one

2-(3-Cyclopentyloxy-4-methoxyphenyl)-1,1-dioxo-1,2-dihydro-1λ^6-isothiazolo[5,4-c]pyridin-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-isothiazolo[5,4-c]pyridin-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-1,2-dihydro-1λ^4-isothiazolo[5,4-c]pyridin-3-one

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1,1-dioxo-1,2-dihydro-1λ^4-isothiazolo[5,4-c]pyridin-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-benzo[d]isothiazol-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-

ylmethyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-benzo[d]isothiazol-3-one

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl]-benzo[d]isothiazol-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

2-[2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl]-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl}-benzo[d]isothiazol-3-one

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl}-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

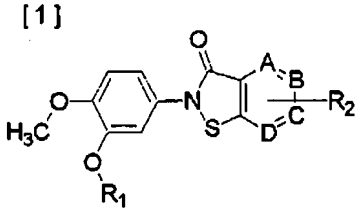
2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-6-ylmethyl}-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

The compounds of the present invention are useful in the form of the acid, or N-oxide thereof or in the form of a pharmaceutically acceptable salt thereof. All forms are within the scope of the invention. Pharmaceutically acceptable salts within the scope of the invention are those derived from the following acids; mineral acids

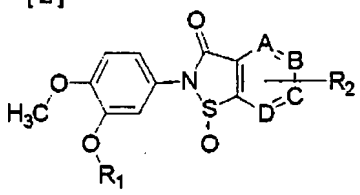
such as hydrochloric acid, sulfuric acid, phosphoric acid and sulfamic acid; organic acids such as acetic acid, citric acid, lactic acid, tartaric acid, malonic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and *p*-toluenesulfonic acid, cyclohexylsulfamic acid, quinic acid, and the like.

This invention relates to the synthesis and preparation method of the novel 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives. According to this invention, the compound of formula [5] is prepared by oxidation of benzo[1,2]dithiol-3-one derivatives. The compound of formula [1] is prepared by the reaction with the compound of formula [4] and the compound of formula [5]. The compound of formula [2] and [3] is prepared by oxidation of the compound of formula [1], in which one of A, B, C and D is nitrogen. By this way, the 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives can be prepared.

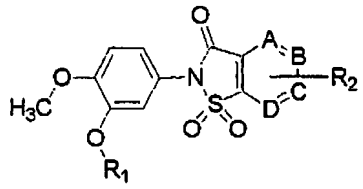
[1]



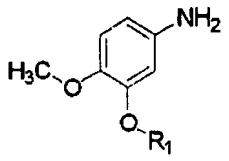
[2]



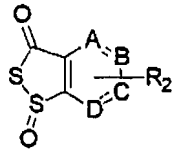
[3]



[4]



[5]

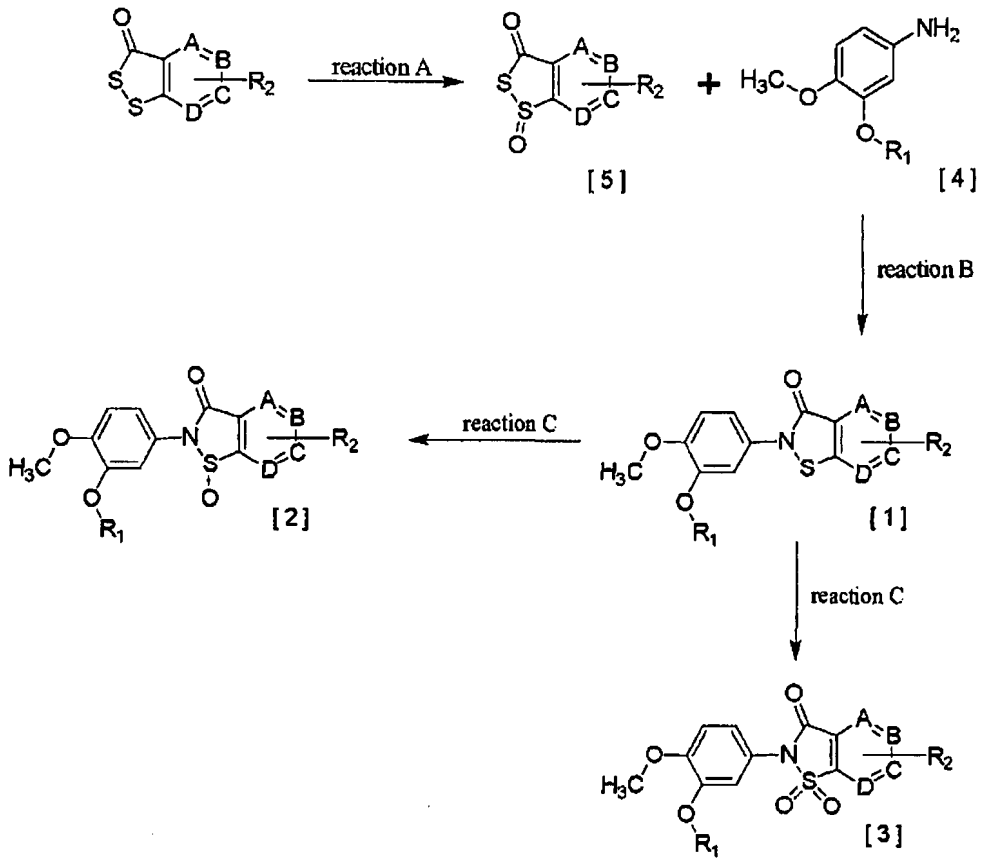


Wherein,

A, B, C, D, R1, and R2 are as defined above.

The preparation for the compound of formula [1] in this invention can be described in the following reaction scheme 1.

[Scheme 1]



Wherein,

A, B, C, D, R1, and R2 are as defined above.

In the following, the preparation of 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives of formula [1] is described in detail.

isothiazolinone derivatives of formula [1] is described in detail.

In the reaction A, the compound of formula [5] is prepared by oxidation of benzo[1,2]dithiol-3-one derivatives with hydrogen peroxide in the acidic catalyst at ranging 20-40℃ for 4-48 hours. The catalyst is acetic acid, hydrochloric acid, sulfuric acid, nitric acid, or trifluoroacetic acid. Acetic acid is most preferably used among these catalysts. The reaction of formula [5] with [4] in unreactive solvent at room temperature (rt) for 2~8h is afforded to the compound of formula [1]. Unreactive solvent such as chloroform, dichloromethane, acetonitrile, tetrahydrofuran, benzene and toluene can desirably be used and dichloromethane is most preferable among these solvents. The compound of formula [2] and [3] is prepared by oxidation of the compound of formula [1] with oxidizing agent at –50 ~ 20℃ for 1-4 hours, in which one of A, B, C and D is nitrogen. The oxidizing agent is hydrogen peroxide, *m*-chloroperoxybenzoic acid (*m*-CPBA), tetrabutylammonium peroxydisulfate, sodium metaperiodate, and trifluoromethanesulfonic anhydride. *m*-CPBA is most preferable among these agents. By this way, the 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives can be prepared.

The 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone compounds of formula [1], [2], and [3] prepared from the above method can be separated and purified by general method such as column chromatography, or recrystallization.

The novel 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone compounds of formula [1], [2], and [3] in this invention can inhibit the action of detrimental excess of TNF-α and hence can prevent and treat various diseases such as joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, allergic inflammation and autoimmune disease. The representative compounds of this invention such as compound 7, 9 and 13 in Table 1 showed the oral median lethal dose of more than 3.5g per Kg of body weight in Table 4 which suggests that these compounds are acceptably non-toxic for pharmaceutical use. Therefore, in order to use compounds of formula [1] or pharmaceutically acceptable salt thereof for therapeutic purposes, it will normally be formulated into a

pharmaceutical composition in accordance with standard pharmaceutical practice. This invention, therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of formula [1] and a pharmaceutically acceptable carrier or diluent.

The composition in this invention can be mixed in general pharmaceutical method with pharmaceutically acceptable carrier to give variety of useful pharmaceutical formulations for oral administration such as tablet, capsule, granules, powders, aqueous solutions or suspensions; for injection such as injectable solutions, suspended solutions; for local administration such as suppositories, ointments, creams, gel, spray and patches.

The products according to the invention may be presented in forms permitting administration by the most suitable route and the invention also relates to pharmaceutical compositions containing at least one product according to the invention which are suitable for use in human or veterinary medicine. These compositions may be prepared according to the customary methods, using one or more pharmaceutically acceptable adjuvants or excipients. The adjuvants comprise, inter alia, diluents, sterile aqueous media and the various non-toxic organic solvents. The compositions may be presented in the form of tablets, pills, granules, powders, aqueous solutions or suspensions, injectable solutions, elixirs or syrups, and can contain one or more agents chosen from the group comprising sweeteners, flavorings, colorings, or stabilizers in order to obtain pharmaceutically acceptable preparations. The choice of vehicle and the content of active substance in the vehicle are generally determined in accordance with the solubility and chemical properties of the product, the particular mode of administration and the provisions to be observed in pharmaceutical practice. For example, excipients such as lactose, sodium citrate, calcium carbonate, dicalcium phosphate and disintegrating agents such as starch, alginic acids and certain complex silicates combined with lubricants such as magnesium stearate, sodium lauryl sulfate and talc may be used for preparing tablets. To prepare a capsule, it is advantageous to use lactose and high molecular weight polyethylene glycols. When aqueous suspensions are used they can contain

emulsifying agents or agents which facilitate suspension. Diluents such as sucrose, ethanol, polyethylene glycol, propylene glycol, glycerol and chloroform or mixtures thereof may also be used. For parenteral administration, emulsions, suspensions or solutions of the products according to the invention in vegetable oil, for example sesame oil, groundnut oil or olive oil, or aqueous-organic solutions such as water and propylene glycol, injectable organic esters such as ethyl oleate, as well as steril aqueous solutions of the pharmaceutically acceptable salts, are used. The solutions of the salts of the products according to the invention are especially useful for administration by intramuscular or subcutaneous injection. The aqueous solution, also comprising solutions of the salts in pure distilled water, may be used for intravenous administration with the proviso that their pH is suitably adjusted, that they are judiciously buffered and rendered isotonic with a sufficient quantity of glucose or sodium chloride and that they are sterilized by heating, irradiation or microfiltration. Suitable compositions containing the compounds of the invention may be prepared by conventional means. For example, compounds of the invention may be dissolved or suspended in a suitable carrier for use in a nebulizer or a suspension or solution aerosol, or may be absorbed or adsorbed onto a suitable solid carrier for use in a dry powder inhaler. Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing at least one compound of formula [1]. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from 0.001 to 50, preferably 0.001 to 5mg/kg body weight per day by inhalation, from 0.01 to 100, preferably 0.1 to 70, more especially 0.5 to 10mg/kg body weight per day by oral administration, and from 0.001 to 10, preferably 0.01 to 1mg/kg body weight per day by intravenous administration. In each particular case, the doses will be determined in accordance with the factors distinctive to the subjects to be treated, such as age, weight, general state of health and other characteristics that can influence the efficacy of the medicinal product. The products according to the invention may be administered as frequency as necessary

in order to obtain the desired therapeutic effect. It may be necessary to have long-term treatments at the rate of 1 to 4 doses per day, in accordance with the physiological requirements of each particular patient. Generally, the active product may be administered orally 1 to 4 times per day.

The following examples represent this invention and this invention is not limited in only these examples.

EXAMPLES

Reference Example 1

3-Cyclopentyloxy-4-methoxynitrobenzene

To a solution of 2-methoxy-5-nitrophenol (3.0g, 17.74mmol) in DMF (30ml) were added cyclopentyl bromide (4.0g, 26.61 mmol) and potassium carbonate (5.0g, 35.48mmol). The reaction mixture was stirred at 60℃ for 15h, cooled to rt, treated with distilled water (20ml), and extracted twice with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound (4.0g, 95%) as a pale yellow solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.65-1.68(m, 2H), 1.86-2.02(m, 6H), 3.95(s, 3H), 4.87(m, 1H), 6.9(d, J=8.9Hz, 1H), 7.74(d, J=2.6Hz, 1H), 7.87-7.91(dd, J=2.6, 8.9 Hz, 1H).

Reference Example 2

3-Cyclopentyloxy-4-methoxyaniline

To a solution of 3-cyclopentyloxy-4-methoxynitrobenzene (4.2g, 17.7mmol) in methanol (30ml) were added ammonium formate (3.5g, 53.2 mmol) and 10% Pd-C (0.3g). The reaction mixture was refluxed for 2h, cooled to rt, filtered through Celite, and evaporated *in vacuo* to remove solvent. The residue was dissolved in ether, washed twice with distilled water, dried over $MgSO_4$, filtered, and

concentrated *in vacuo* to give the title compound (3g, 81%) as pale brown liquid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-1.63(m, 2H), 1.85-1.95(m, 6H), 3.05(bs, 2H), 3.78(s, 3H), 4.73(m, 1H), 6.24(dd, J=2.6, 8.4Hz, 1H), 6.33(d, J=2.6Hz, 1H), 6.73(d, J=8.4Hz, 1H).

Reference Example 3

N-(3-Cyclopentyloxy-4-methoxyphenyl)isoindolin-1,3-dione

To a solution of 3-cyclopentyloxy-4-methoxyaniline (0.52g, 2.42mmol) in chloroform (10ml) was added phthalic anhydride (0.36g, 2.43mmol). The reaction mixture was stirred for 0.5h at rt, treated with acetic acid (10ml), refluxed for 4h, cooled to rt, and then concentrated *in vacuo* to remove chloroform and acetic acid. The residue was crystallized from methanol to afford the title compound (0.75g, 91%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-1.64(m, 2H), 1.82-1.96(m, 6H), 3.90(s, 3H), 4.78(m, 1H), 6.96-7.00(m, 3H), 7.77-7.80(m, 2H), 7.93-7.96(m, 2H).

Reference Example 4

2-(3-Cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1,3-dione

To a solution of pyridine-3,4-dicarboxylic acid (1.62g, 9.65mmol) in toluene (10ml) was added thionyl chloride (3.45g, 28.95mmol). The reaction mixture was refluxed for 4h, evaporated *in vacuo* to remove thionyl chloride. To the residue were added dichloromethane (10ml), 3-cyclopentyloxy-4-methoxyaniline (2g, 9.65mmol) and triethylamine (2.44g, 25.13mmol), stirred for 6h at rt, and then concentrated *in vacuo*. The resultant mixture was treated with chloroform (10ml) and acetic acid (2ml), refluxed for 48h, cooled to rt, concentrated *in vacuo* to remove chloroform and acetic acid, added ethanol, and stirred at rt. The resultant solids were filtered to give the title compound (2.8g, 86%) as a yellow solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-2.05(m, 8H), 3.90(s, 3H), 4.75(m, 1H), 6.92(d, J=8.5Hz, 1H), 7.07(m, 2H), 7.44(dd, J=7.8, 4.8Hz, 1H), 8.10(dd, J=7.8, 1.5Hz, 1H), 8.72(dd, J=4.8, 1.5Hz, 1H).

Reference Example 5

N4-(3-Cyclopentyloxy-4-methoxyphenyl)-3-(hydroxymethyl) isonicotinamide

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridin-1,3-dione (0.5g, 1.48mmol) in methanol (10ml) was slowly added sodium borohydride (0.28g, 7.41mmol) at rt. The reaction mixture was stirred for 1h at rt, evaporated *in vacuo*, added distilled water (10ml), and extracted twice with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica to afford the title compound (0.25g, 50%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-2.05(m, 8H), 3.85(s, 3H), 4.52(s, 1H), 4.74(d, J=4.5Hz, 1H), 4.79(m, 1H), 6.84(d, J=8.5Hz, 1H), 7.07(dd, J=8.5, 2.1Hz, 1H), 7.38(m, 2H), 8.61(d, J=4,8Hz, 1H), 8.86(s, 2H).

Reference Example 6

2-(3-Cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

To a solution of N4-(3-cyclopentyloxy-4-methoxyphenyl)-3-(hydroxymethyl)-isonicotinamide (0.4g, 1.17mmol) in anhydrous THF (10ml) were added triphenylphosphine (0.37g, 1.41mmol) and diethylazodicarboxylate (0.25g, 1.41mmol) at rt. The reaction mixture was stirred for 1h at rt, evaporated *in vacuo*, treated with 6N HCl solution (10ml), and extracted with ethyl acetate. The aqueous layer was basified to pH 8-9 with 6N NaOH solution, and extracted with ethyl acetate. Then, the resultant organic layer was dried over $MgSO_4$, filtered, and

concentrated *in vacuo* to give the title compound (0.34g, 89%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-2.05(m, 8H), 3.88(s, 3H), 4.85(m, 1H), 4.87(s, 2H), 6.91(d, J=8.5Hz, 1H), 7.02(dd, J=8.5, 2.1Hz, 1H), 7.51(d, J=5.1Hz, 1H), 7.82(d, J=2.1Hz, 1H), 8.82(d, J=5.1Hz, 1H).

Reference Example 7

6-(Aminomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-6-hydroxymethyl-1-isoindolinone (0.86g, 2.42mmol) in dichloromethane (10ml) were slowly added methane sulfonylchloride (0.33g, 2.90mmol) and triethylamine (0.37g, 3.63mmol) at 0℃. The reaction mixture was stirred for 0.5h at rt, washed twice with distilled water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give [2-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-5-isoindolyl]methyl ethanesulfonate (0.96g, 96%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.61-1.66(m, 2H), 1.83-2.06(m, 6H), 3.02(s, 3H), 3.88(s, 3H), 4.87(s, 2H), 4.86-4.89(m, 1H), 5.36(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.04(dd, J=8.7, 2.5Hz, 1H), 7.58(d, J=7.8Hz, 1H), 7.68(dd, J=7.8, 1.5Hz, 1H), 7.85(d, J=2.5Hz, 1H), 7.96(s, 1H).

To a solution of [2-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-5-isoindolinyl]methyl methanesulfonate (1.0g, 2.42mmol) in DMF (10ml) was added sodium azide (0.47g, 7.26mmol). The reaction mixture was stirred for 2h at 60℃, cooled to rt, added ethyl acetate, washed three times with distilled water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 6-(azidomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone (0.9g, 97%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.61-1.66(m, 2H), 1.86-2.07(m, 6H), 3.89(s, 3H), 4.48(s, 2H), 4.85(s, 2H), 4.86-4.90(m, 1H), 6.91(d, J=8.7Hz, 1H), 7.04(dd, J=8.7, 2.5Hz, 1H), 7.56(m, 2H), 7.86(m, 2H).

To a solution of 6-(azidomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-

isoindolinone (0.92g, 2.42mmol) in THF (10ml) was added triphenylphosphine (0.7g, 2.66mmol). The reaction mixture was stirred for 20min., added distilled water (1ml), stirred for 8h at rt, added 1N HCl solution, and extracted with ethyl acetate. The aqueous layer was basified to pH 8-9 with 2N NaOH solution, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound (0.79g, 92%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.56-1.66(m, 2H), 1.85-2.07(m, 6H), 3.88(s, 3H), 4.01(s, 2H), 4.83(s, 2H), 4.82-4.89(m, 1H), 6.90(d, J=8.7Hz, 1H), 7.05(dd, J=8.7, 2.5Hz, 1H), 7.48(m, 1H), 7.58(d, J=7.7Hz, 1H), 7.87(m, 2H).

Example 1

1-Methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene

The title compound was prepared following the procedures described in reference example 1 with 4-phenyl-butan-2-ol (0.89g, 5.92mmol) as a pale yellow solid (1.64g, 92%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.39(d, J=6.1Hz, 3H), 1.94-2.13(m, 2H), 2.83(m, 2H), 3.90(s, 3H), 4.40(m, 1H), 6.92(d, J=8.8Hz, 1H), 7.17-7.28(m, 5H), 7.48(d, J=5.1 Hz, 1H), 7.72(d, J=2.6Hz, 1H).

Example 2

4-Methoxy-3-(1-methyl-3-phenyl-propoxy)aniline

The title compound was prepared following the procedures described in reference example 2 with 1-methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene (1.5g, 4.98mmol) as a pale yellow solid (1.09g, 81%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.39(d, J=6.1Hz, 3H), 1.93-2.12(m, 2H), 2.81(m, 2H), 3.87 (b, 2H), 3.88(s, 3H), 4.41(m, 1H), 6.91(d, J=8.8Hz, 1H), 7.15-7.24(m, 5H), 7.46(d, J=5.1 Hz, 1H), 7.70(d, J=2.6Hz, 1H).

Example 3

1-Oxo-1*H*-1λ^4-benzo[1,2]dithiol-3-one

To a solution of benzo[1,2]dithiol-3-one (5.0g, 29.72mmol) in acetic acid (40ml) was slowly added hydrogen peroxide (5.06ml) under nitrogen atmosphere. The reaction mixture was stirred overnight at rt, filtered, added ice-crake into the filtercake, and filtered the precipitate. The filtercake was dissolved in dichloromethane (15ml), washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the title compound (4.1g, 75%) as a yellowish solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 7.46(t, J=7.0Hz, 1H), 7.58(d, J=8.0Hz, 1H), 7.66(t, J=6.1Hz, 1H), 8.10(d, J=7.8Hz, 1H).

Example 4

6-Aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isoindol-1-one

The title compound was prepared following the procedures described in example 2 and reference example 7 with 1-methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene (1.5g, 4.98mmol) as a pale yellow solid (1.09g, 81%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.38(d, J=6.1Hz, 3H), 1.95-2.12(m, 2H), 2.83(m, 2H), 3.86(b, 2H), 3.88(s, 3H), 4.41(m, 1H), 4.83(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.02(dd, J=8.7, 2.5Hz, 1H), 7.15-7.24(m, 5H), 7.46(m, 1H), 7.59(d, J=7.7Hz, 1H), 7.87(m, 2H).

Example 5

6-Aminomethyl-2-(3-cyclopentyloxy-4-methoxyphenyl)-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 2 and reference example 7 with 1-methoxy-2-(1-methyl-3-phenyl-

propoxy)-4-nitrobenzene (1.5g, 4.98mmol) as a pale yellow solid (1.09g, 81%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.38(d, J=6.1Hz, 3H), 1.95-2.12(m, 2H), 2.83(m, 2H), 3.86(b, 2H), 3.88(s, 3H), 4.41(m, 1H), 4.83(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.02(dd, J=8.7, 2.5Hz, 1H), 7.46(m, 1H), 7.59(d, J=7.7Hz, 1H), 7.87(m, 2H).

Example 6

6-Aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-pyrrolo[3,4-c]pyridin-1-one

The title compound was prepared following the procedures described in example 2 and reference example 7 with 1-methoxy-2-(1-methyl-3-phenyl-propoxy)-4-nitrobenzene (1.5g, 4.98mmol) as a pale yellow solid (1.09g, 81%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.38(d, J=6.1Hz, 3H), 1.95-2.12(m, 2H), 2.83(m, 2H), 3.86(b, 2H), 3.88(s, 3H), 4.41(m, 1H), 4.83(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.02(dd, J=8.7, 2.5Hz, 1H), 7.15-7.24(m, 5H), 7.46(m, 1H), 7.59(d, J=7.7Hz, 1H), 7.87(m, 2H).

Example 7

2-(3-Cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one

To a solution of 6-(aminomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone (0.92g, 2.61mmol) in dichloromethane (20ml) was added 1-oxo-1*H*-1λ^4-benzo[1,2]dithiol-3-one (0.43g, 2.37mmol). The reaction mixture was stirred for 3h at rt under nitrogen atmosphere, extracted with 10% HCl solution. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash chromatography on silica to give the title compound (0.81g, 76%) as a yellowish solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.60-2.02(m, 8H), 3.90(s, 3H), 4.83(m, 1H), 6.93(d, J=8.7Hz, 1H), 7.10(dd, J=8.7, 2.5Hz, 1H), 7.32(d, J=2.5Hz, 1H), 7.46(t, J=7.0Hz, 1H), 7.58(d, J=8.0Hz, 1H), 7.66(t, J=6.1Hz, 1H), 8.10(d, J=7.8Hz, 1H).

Example 8

2-(3-Cyclopentyloxy-4-methoxyphenyl)-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one (0.5g, 1.46mmol) in dichloromethane (10ml) was added the solution of *m*-CPBA (0.25g, 1.46mmol) in dichloromethane (3ml) at -50℃. The reaction mixture was stirred for 30min at -50℃ under nitrogen atmosphere, washed with water and then 1N NaOH solution. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and recrystallized from ether to give the title compound (0.48g, 92%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.59-1.98(m, 8H), 3.91(s, 3H), 4.79(m, 1H), 6.95-7.07(m, 3H), 7.82-7.88(m, 2H), 7.97(d, J=6.9Hz, 1H), 8.10(d, J=6.6Hz, 1H).

Example 9

2-(3-Cyclopentyloxy-4-methoxyphenyl)-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

To a solution of 2-(3-cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one (0.5g, 1.46mmol) in dichloromethane (10ml) was added the solution of *m*-CPBA (0.75g, 4.38mmol) in dichloromethane (3ml) at -20℃. The reaction mixture was warmed to 0℃ under nitrogen atmosphere, washed with water and then 1N NaOH solution. The organic layer was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and recrystallized from ether to give the title compound (0.44g, 81%) as a white solid.

^{1}H-NMR($CDCl_3$, ppm) : δ 1.58-1.99(m, 8H), 3.92(s, 3H), 4.79(m, 1H), 6.93-7.0(m, 2H), 7.09(dd, J=8.7, 2.5Hz, 1H), 7.89-7.95(m, 2H), 8.01(d, J=6.9Hz, 1H), 8.18(d, J=6.6Hz, 1H).

Example 10

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 2 and 7 with 4-methoxy-3-(1-methyl-3-phenyl-propoxy)aniline (1.0g, 3.69mmol) as a yellowish solid (1.21g, 81%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.32(d, J=6.1Hz, 3H), 1.96-2.12(m, 2H), 2.82(m, 2H), 3.88(s, 3H), 4.40(m, 1H), 4.83(m, 1H), 6.93(d, J=8.7Hz, 1H), 7.10(dd, J=8.7, 2.5Hz, 1H), 7.16-7.24(m, 5H), 7.32(d, J=2.5Hz, 1H), 7.46(t, J=7.0Hz, 1H), 7.58(d, J=8.0Hz, 1H), 7.66(t, J=6.1Hz, 1H), 8.10(d, J=7.8Hz, 1H).

Example 11

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 8 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-benzo[d]isothiazol-3-one (0.5g, 1.23mmol) as a white solid (0.45g, 87%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.33(d, J=6.1Hz, 3H), 1.95-2.12(m, 2H), 2.81(m, 2H), 3.87(s, 3H), 4.41(m, 1H), 4.83(m, 1H), 6.91(d, J=8.7Hz, 1H), 7.08(dd, J=8.7, 2.5Hz, 1H), 7.18-7.24(m, 5H), 7.31(d, J=2.5Hz, 1H), 7.89-7.95(m, 2H), 8.01(d, J=6.9Hz, 1H), 8.18(d, J=6.6Hz, 1H).

Example 12

2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 9 with 2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-

benzo[d]isothiazol-3-one (0.5g, 1.23mmol) as a white solid (0.42g, 78%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.34(d, J=6.1Hz, 3H), 1.99-2.12(m, 2H), 2.83(m, 2H), 3.89(s, 3H), 4.43(m, 1H), 4.85(m, 1H), 6.92(d, J=8.7Hz, 1H), 7.10(dd, J=8.7, 2.5Hz, 1H), 7.15-7.24(m, 5H), 7.35(d, J=2.5Hz, 1H), 7.86-7.95(m, 2H), 8.02(d, J=6.9Hz, 1H), 8.16(d, J=6.6Hz, 1H).

Example 13

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 7 with 6-(aminomethyl)-2-(3-cyclopentyloxy-4-methoxyphenyl)-1-isoindolinone (0.5g, 1.42mmol) as a yellowish solid (0.53g, 76%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.62-2.05(m, 8H), 3.85(s, 3H), 4.79(s, 2H), 4.83(m, 1H), 5.15(s, 2H), 6.88(d, J=8.7Hz, 1H), 7.00(dd, J=8.7, 2.5Hz, 1H), 7.42-7.61(m, 5H), 7.84(d, J=2.2Hz, 2H), 8.08(d, J=7.9Hz, 1H).

Example 14

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 8 with 2-[2-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one (0.5g, 1.03mmol) as a white solid (0.46g, 89%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.61-2.05(m, 8H), 3.87(s, 3H), 4.83(s, 2H), 4.85(m, 1H), 4.92(d, J=15.7Hz, 1H), 5.38(d, J=15.7Hz, 1H), 6.89(d, J=8.7Hz, 1H), 7.01(dd, J=8.7, 2.5Hz, 1H), 7.52(d, J=7.8Hz, 1H), 7.67-8.05(m, 7H).

Example 15

2-[2-(3-Cyclopentyloxy-4-methoxy-phenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 9 with 2-[2-(3-cyclopentyloxy-4-methoxyphenyl)-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl]-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one (0.5g, 1.03mmol) as a white solid (0.42g, 79%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.62-2.05(m, 8H), 3.87(s, 3H), 4.82(s, 2H), 4.87(m, 1H), 5.18(s, 2H), 6.89(d, J=8.7Hz, 1H), 7.02(dd, J=8.7, 2.5Hz, 1H), 7.44-7.63(m, 5H), 7.85(m, 2H), 8.10(d, J=7.9Hz, 1H).

Example 16

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 7 with 6-aminomethyl-2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-2,3-dihydro-isoindol-1-one (0.5g, 1.20mmol) as a yellowish solid (0.57g, 87%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.34(d, J=6.1Hz, 3H), 1.99-2.12(m, 2H), 2.83(m, 2H), 3.87(s, 3H), 4.48(m, 1H), 4.78(s, 2H), 4.85(m, 1H), 5.16(s, 2H), 6.94(d, J=8.7Hz, 1H), 7.02(dd, J=8.7, 2.5Hz, 1H), 7.15-7.28(m, 5H), 7.42-7.61(m, 5H), 7.84(d, J=2.2Hz, 2H), 8.08(d, J=7.9Hz, 1H).

Example 17

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-1-oxo-1,2-dihydro-1λ^4-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in

example 8 with 2-{2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-benzo[d]isothiazol-3-one (0.5g, 0.91mmol) as a white solid (0.42g, 82%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.35(d, J=6.1Hz, 3H), 1.95-2.12(m, 2H), 2.85(m, 2H), 3.89(s, 3H), 4.47(m, 1H), 4.85(s, 2H), 4.87(m, 1H), 4.93(d, J=15.7Hz, 1H), 5.39(d, J=15.7Hz, 1H), 6.92(d, J=8.7Hz, 1H), 7.03(dd, J=8.7, 2.5Hz, 1H), 7.15-7.28(m, 5H), 7.52(d, J=7.8Hz, 1H), 7.67-8.05(m, 7H).

Example 18

2-{2-[4-Methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-1,1-dioxo-1,2-dihydro-1λ^6-benzo[d]isothiazol-3-one

The title compound was prepared following the procedures described in example 9 with 2-{2-[4-methoxy-3-(1-methyl-3-phenyl-propoxy)-phenyl]-3-oxo-2,3-dihydro-1*H*-isoindol-5-ylmethyl}-benzo[d]isothiazol-3-one (0.5g, 0.91mmol) as a white solid (0.41g, 79%).

^{1}H-NMR($CDCl_3$, ppm) : δ 1.36(d, J=6.1Hz, 3H), 1.97-2.12(m, 2H), 2.86(m, 2H), 3.87(s, 3H), 4.48(m, 1H), 4.86(s, 2H), 4.89(m, 1H), 5.17(s, 2H), 6.91(d, J=8.7Hz, 1H), 7.01(dd, J=8.7, 2.5Hz, 1H), 7.13-7.28(m, 5H), 7.53(d, J=7.8Hz, 1H), 7.69-8.05(m, 7H).

The following Composition Examples illustrate pharmaceutical compositions according to the present invention.

Composition Example 1

2-(3-Cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one (1g) (mean particle size 3.5 microns) and lactose (99g) (mean particle size 72 microns) are blended together for 30 minutes in a mechanical shaker/mixer. The resultant

blend is filled, to a fill weight of 25mg, into No. 3 hard gelatine capsules, to give a product suitable for use, for example, with a dry powder inhaler.

Composition Example 2

No. 2 size gelatine capsules each containing:

2-(3-Cyclopentyloxy-4-methoxyphenyl)-benzo[d]isothiazol-3-one	20mg
Lactose	100mg
Starch	60mg
Dextrin	40mg
magnesium stearate	1mg

are prepared in accordance with the usual procedure.

Compositions similar to those above are prepared from other compounds of formula [1].

Experimental Example 1

TNF-α *in vitro* assay (reference; Taffet S.M. et al., Cellular Immunology (1989) 120, 291-300);

After cancer cell line of mouse macrophage (RAW264.7) is diluted with RPMI1640 medium (containing 5% FCS), then plated out in 24 well plates at 1x106 cells/ml. Then, the culture is incubated for 18 hours at 5% CO_2 and 37℃. 1μM of compound and 1μg/ml of lipopolysaccharide (LPS) are added to the plate and the culture is incubated for 6 hours at 37℃. After incubated, the culture is centrifuged and supernatants are collected. The supernatants are stored at -20℃ till measurement. The measurement of TNF-α in the media is performed with a mouse TNF-α kit (Amersham, UK). And the procedure is in accordance with the guidance provided by

Amersham. Inhibition percentage of each compound is calculated by comparison of amount of TNF-α, released in the well treated with compound, with that in the well without any treatment. Inhibitory activities of compounds on *in vitro* TNF-α synthesis are listed in Table 1. And IC_{50} of the compounds of formula [1] is between 1 and 1000nM.

Table 1

Example No.	% Inhibition
7	68.5
8	45.3
9	80.4
13	58.2
14	49.0
15	54.9

Experimental Example 2

TNF-α *in vivo* assay(reference; Novogrodsky A. et al., Science (1994) 264, 319-322)

After compound is suspended in 5% sodium carboxymethyl cellulose (CMC), starved mouse (C57BL/6, 6-week old, male) is administered orally at the volume of 0.1ml per 10g of body weight. Lipopolysaccharide (LPS) is injected intraperitoneally at the concentration of 1.5mg/mouse for 2 hours after compound administration. The control is administered orally with 5% Na CMC at the volume of 0.1ml per 10g of body weight. After one and half hours, mice are anaesthetized with ether, blood is collected from vena cava and serum is collected from blood after 5-minute centrifugation at 12,000 rpm. The serum collected is stored at -20℃ till TNF-α ELISA assay. The amount of TNF-α in serum is measured with a mouse TNF-α kit (Amersham, UK). And the procedure is in accordance with the guidance provided by Amersham Inhibitory activities of compounds on *in vivo* TNF-α synthesis are listed

in Table 2.

Table 2

Example No.	Control (TNF-α : 1750 pg/ml)	7	9	13
Administration Amount (mg/kg)		10	10	10
Inhibitory Activity (%)		70.2	82.6	65.8

According to Table 1 and Table 2, compounds invented by us, show high inhibitory effect on *in vitro* and *in vivo* TNF-α synthesis.

Experimental Example 3

Assay for PDE 4 inhibitory activity

PDE 4 activity was determined by using partially purified PDE 4 from human monocyte (U937) and [^{3}H]-cAMP (1μM) as the substrate. Human monocyte PDE 4 was isolated as described by Torphy et al. (J. Pharmacol. Exp. Ther., 263, 1195-1205, 1992). Synthetic compounds and rolipram were tested at seven concentrations from 10^{-9} to 10^{-3} M in duplicate. The test compounds and the substrate with U937 cells was incubated at 37℃ for 30 min. The product of reaction ([^{3}H] 5'AMP) was separated from the substrate by elution on cation-exchange columns and radioactivity was determined with a liquid scintillation counter (LS 1701, Beckman) using a liquid scintillation cocktail. IC_{50} values were determined by non-linear regression analysis of the competition curves. Inhibitory activities (IC_{50}) of compounds on *in vitro* PDE 4 are listed in Table 3.

Table 3

Example No.	IC_{50} (μM)
7	0.45
9	0.086
13	0.52

Experimental Example 4

Acute Toxicity Test (LD_{50})

The compounds in Table 3 are administered orally at various dose with SPF ICR mice (body weight 20±1g). The animal number of each group is 5. The number of the dead is checked for 24 hours after administration. And animal condition and the number of the dead have been observed for 7 days. The lethal dose of 50% (LD_{50}) is calculated in accordance with Litchfield-Wilcoxon) method. The result is listed in Table 4.

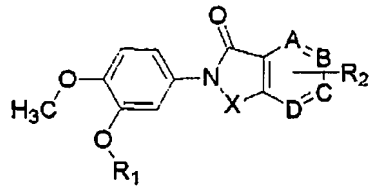
Table 4

No. of compound	Route of Administration	LD_{50} (g/kg)
7	P.O*	> 3.5
9	P.O	> 3.5
13	P.O	> 3.5

* indicates post oral.

WHAT IS CLAIMED IS:

1. A compound of formula 1 wherein,



where in

R1 is lower alkyl, cycloalkyl, hydroxycycloalkyl, arylalkyl, cycloalkylalkyl, bicycloalkyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 wherein,

R1 is C_1-C_4 lower alkyl, C_3-C_6 cycloalkyl, hydroxy C_3-C_6 cycloalkyl, aryl C_3-C_8 alkyl, C_3-C_6 cycloalkyl C_1-C_2 alkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, C_1-C_4 lower alkyl, C_1-C_4 lower alkoxy, amino, C_1-C_4 lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, C_1-C_2 lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 2 wherein,

R1 is methyl, ethyl, propyl, C_3-C_6 cycloalkyl, hydroxy C_3-C_6 cycloalkyl, aryl C_3-C_6 alkyl, C_3-C_5 cycloalkyl C_1-C_2 alkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, methyl, methoxy, amino, methylamino, cyano, aldehyde, aldehydeoxime, -COR3, -CH_2NC(O)(R4)(R5);

R3 is hydroxy, -$NHNH_2$, methyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

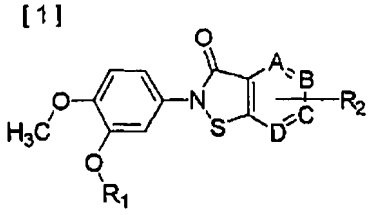
X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

4. A process for preparing 3-cyclopentyloxy-4-methoxyphenyl-isothiazolinone derivatives having the formula [1], which comprises the following procedures. . The compound of formula [1] is prepared by the reaction with the compound of formula [4] and the compound of formula [5]. The compound of formula [2] and [3] is prepared by oxidation of the compound of formula [1], in which one of A, B, C and D is nitrogen.

[1]



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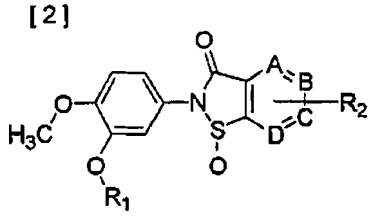

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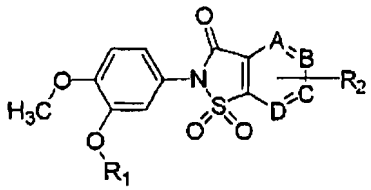

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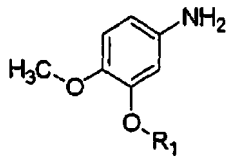
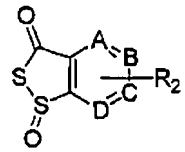


[5]



wherein,

R1 is lower alkyl, cycloalkyl, hydroxycycloalkyl, arylalkyl, cycloalkylalkyl, 1-indanyl or 2-indanyl;

R2 is hydrogen, halogen, hydroxy, methylhydroxy, lower alkyl, lower alkoxy, amino, lower alkylamino, cyano, aldehyde, aldehydeoxime, -COR3, -$CH_2NC(O)(R4)(R5)$;

R3 is hydroxy, -$NHNH_2$, lower alkyl;

R4 is carbonyl, sulfur, sulfoxide, sulfone;

R5 is phenyl, pyridyl;

X is oxygen or carbon, carbonyl, sulfur, sulfoxide, sulfone, selenium, selenium oxide, selenium dioxide;

A, B, C, and D are independently carbon, nitrogen or N-oxide;

or a pharmaceutically acceptable salt thereof.

5. A method for treating a disease state capable of being modulated by inhibiting TNF-α comprising administering to a patient suffering from said disease state an

effective amount of the compound of claim 1.

6. The method of claim 5, wherein said disease state is an inflammatory disease or autoimmune disease.

7. The method of claim 5, wherein said disease state is selected from the group consisting of joint inflammation, rheumatoid arthritis, osteoarthritis, sepsis, septic shock, asthma, graft versus host reaction, psoriasis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, multiple sclerosis, type I diabetes mellitus, chronic glomerulonephritis, and inflammatory bowel disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR01/00579

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 209/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)
IPC7 : C07D 209/46, C07D 275/02, A61K 31/425

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched
Korean Patents and application for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search trerms used)
MEDLINE, NPS, PAJ, STN on line

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9842666 A (DAEWOONG PHARMACEUTICAL CO., LTD.) 01 OCT 1998 see the whole document	1-3, 5-7
X	Arch. Pharm. Res., vol. 23, no. 4, pp. 332-337 (2000) see the whole document	1-3, 5-7
A	US 6180644 B (CELGENE CORP.) 30 JAN 2001 claims 1, 10, 11	1-7
A	WO 9202220 A (SMITHKLINE BEECHAM CORP.) 20 FEB 1992 claims 1-10, 20	1-7
A	WO 9219594 A (SMITHKLINE BEECHAM CORP.) 12 NOV 1992 claims 1-12	1-7
A	WO 9722585 A (MERCK FROSST CANADA INC.) 26 JUN 1997 claims 1, 11-15	1-7

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevence
"E" earlier application or patent but published on or after the international filing date
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"P" document published prior to the international filing date but later than the priority date claimed
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"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 DECEMBER 2001 (28.12.2001)	28 DECEMBER 2001 (28.12.2001)

Name and mailing address of the ISA/KR	Authorized officer
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Facsimile No. 82-42-472-3556	Telephone No. 82-42-481-5600

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR01/00579

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